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Serum Uric Acid Levels as a Prognostic Marker in Acute Heart Failure Patients

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ABSTRACT

Background: According to latest epidemiological and clinical research, serum uric acid can be one of the helpful indicators in determining the risk of mortality in acute heart failure. This study's purpose is to correlate serum uric acid levels in patients with AHF and assess the prognostic relevance of SUA levels in those individuals.

Aim & Objectives: The study's main purpose is to see if serum uric acid levels could be used as a prognostic indicator in patients with acute heart failure. The study also focusses on the clinical profile of individuals with AHF as well as the amount of serum uric acid in AHF patients, the relation between serum uric acid levels, hospital stay length and mortality rate after release; and the risk variables associated with death in AHF patients.

Methods: The study will be a nine-month cross-sectional study with a six-month follow-up from June 2021 to February 2022. The study will enroll approximately 253 patients with AHF, both new-onset and acute decompensation of chronic heart failure, in the hospital's Medicine ICU.

Conclusion: The measurement of SUA levels may help to confirm the risk of unfavourable outcomes in patients with AHF. The reduction of uric acid can be expected to be a novel strategy to HF prevention and treatment.

Key words: Serum uric acid, Acute heart failure, Hyperuricemia

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INTRODUCTION

Heart failure (HF) is as a clinical condition explained by current or previous complaints like breathlessness, ankle swelling, and tiredness, along with signs like elevated JVP, pulmonary crepitation's, and peripheral oedema, all of which are caused by an anatomical and/or physiological cardiac abnormality and confirmed by at least 1 of the following: raised BNP levels or verifiable evidence of respiratory, cardiac or systemic congestion [1]. Acute heart failure (AHF) is a life-threatening medical illness with abrupt onset or deterioration of HF symptoms and signs, necessitating urgent medical aid [2]. AHF may be due to primary cardiac disorders like CAD, CMP, valvular diseases, etc. or exacerbated by extrinsic risk factors like hypothyroidism, anaemia etc.. [3]. According to Huffman & Prabhakaran et al, Heart failure affects between 1.3 and 4.6 million people in India each year, with an annual incidence of 491 600–1.8 million [4]. Several studies have found that the age at which South Asians, particularly Indians, develop heart failure is much lower than in the western population [5-7]. AHF is among the foremost cardiac causes of hospital admissions in patient's ≥ the age of 65 within the developed world. Various small studies and data of established risk factors imply that the affliction of HF is between 2 and 5 million people in India, with an approximated frequency of 1.2/1000 population [8,9].

As AHF is a common fatal threat, the proficiency to predict the prognosis is necessary for ideal management of patients. Biomarkers like Brain Natriuretic Peptide (BNP) are being practiced as a prognostic marker clinically. Even though BNP are useful prognostic markers they are not easily available and affordable in the rural Indian populations. In this setting, there is a need for readily available and affordable biomarkers for

predicting the prognosis i.e., mortality and readmission in AHF. SUA is noticed as a prognostic biomarker among patients of cardiac failure [10]. The enzyme xanthine oxidase produces uric acid (UA), a by-product of purine metabolism (XO). Elevated uric acid in the blood is frequent in patients with HF. Other factors also contribute to increasing SUA in HF apart from xanthine oxidase activity like hypoxia and muscle catabolism. Xanthine oxidase is liable for the generation of toxic oxidant products and consequently, more elevated serum uric acid levels cause greater oxidant formation. Increased oxidant production leads to various detrimental effects like oxidative stress, reduced contractility, inflammatory reactions, mitochondrial or endothelial instability, and metabolic inefficiency. Studies have shown that increased XO activity will be allied with loss of function leading to cardiac arrest as well as poor results in HF patients [11]. Coiro, et al. [11], in their 310 acute heart failure patients found that Hyperuricemia will be associated with high mortality and readmission. Okazaki, et al. [12], in their 899 AHF patients showed that serum uric acid will be an unconventional analyst of mortality at 180 days. As mentioned above, the majority of the studies have been done among acute heart failure patients from the western population. Furthermore, no studies have been done on the rural Indian population. If found to possess a predictive impact in acute heart failure patients, serum uric acid may act as a cheaper biomarker than NT pro-BNP in rural areas of India where NT pro-BNP is not readily available, affordable and accessible. Hence, we aim to analyze the influence of uric acid levels in serum as a prognostic predictor in Indian patients admitted to ICU having features of AHF.

Aim and objectives

Aim

To study the serum uric acid levels as a prognostic marker in acute heart failure patients.

Objectives

To assess the clinical profile of AHF patients like risk factors, aetiology, treatment given and outcome.

To determine serum uric acid levels among acute heart failure patients.

To study the correlation of serum uric acid levels with the duration of hospitalization and mortality at six months after release.

To determine the risk variables linked to death in patients with acute heart failure.

MATERIALS AND METHODS

Study setting

The research will take place in the Medicine ICU of the Acharya Vinoba Bhave Rural Hospital (AVBRH), a tertiary care teaching hospital in Wardha region. The selected hospital, AVBRH, is a 1200-bedded teaching hospital along with 30 bedded medicine ICU, catering to the needy and rural people of central India.

Type of study

A cross-sectional study with a six-month follow-up will be conducted.

Study period

The study will be conducted for nine months from June 2021 to February 2022. The last patient enrolled in our study will be on 28th February 2022.

Study participants

The study will cover cases of acute heart failure, both new-onset and acute decompensation of chronic heart failure, admitted to this hospital's Medicine ICU.

Inclusion criteria

Cases

Patients clinically diagnosed with acute heart failure according to "Framingham criteria" (Annexure 4) and confirmed on 2d echo and chest radiography.

Age: More than 18 years.

Gender: Males and females.

Consent: Persons who are voluntarily willing and capable of giving consent will be enrolled in the study.

Exclusion criteria

All the conditions that may increase serum uric acid levels like

Chronic renal failure (sr. creatinine >2 mg/dl/GFR <60ml/min)

Haematological malignancies

Already diagnosed hyperuricemic patients

Patients on drugs that increase serum uric acid levels (cyclophosphamide, cyclosporine, ethacrynic acid, ethambutol)

All the patients who are on urate-lowering drugs like allopurinol, febuxostat.

Chronic obstructive pulmonary disease with Cor pulmonale.

Follow up

All the patients of AHF fulfilling the inclusion criteria will be followed up telephonically or interviewed (in Medicine OPD) every two months for the next six months from the date of discharge. They will be monitored for death.

Sample size

Cases

$n=Z2P(1-P)/d^2$

Where Z is the level of confidence i.e., 1.96;

P=Prevalence=15;

D=Desirable precision=5%

Considering the prevalence of Hyperuricemia as 15% in cardiovascular disease, 95% confidence interval, at 5% level of significance and absolute precision of 5% the desired minimum sample size will be 196. We will be taking 253 patients in our study.

Ethics approval

The study will be commenced once the Institutional Ethics Committee at DMIMS (DU), Sawangi (M), Wardha has given its approval.

Data collection

Patients with acute cardiac failure, both new-onset and acute decompensation of chronic heart failure attending AVBRH will be interviewed with the help of the questionnaire. Informed written consent will be taken in the mother tongue, and confidentiality will also be maintained. Participants will be interviewed in the local language (Marathi) and they will be followed up telephonically or interviewed in Medicine OPD every two months for the next six months from the date of discharge.

A questionnaire will be designed to collect information regarding the study. The questionnaire will be pilot tested before data collection. Participant's socio-demographic data and phone numbers, history of circulatory disease, predisposing factors like age, gender, DM, systemic hypertension, history of alcohol, and tobacco use (all forms), and symptoms of heart failure will be recorded. The laboratory parameters, treatment history during the hospital stay and outcome of patients during the hospital stay will be noted.

Then patients will undergo anthropometric measurements like waist circumference, neck circumference, height, weight, BMI, and vitals like blood pressure and pulse. JVP will also be examined.

Examination of patients for heart rate, abnormal heart sounds, and murmurs will be done by doing a detailed clinical cardiovascular examination. The respiratory system examination will be done to look for fine inspiratory crackles. Per abdominal examination will be done to look for free fluid in the abdomen and to look for hepatomegaly.

Within 30 minutes of hospital admission, Serum uric acid, and electrocardiogram (ECG) will be performed. The patient will undergo 2D echocardiography (ECHO) within 12 hours of hospital admission.

All patients will be subjected to studies such as complete blood count (CBC), liver function test (LFT), kidney function test (KFT), creatine kinase MB(CKMB), Troponin- I, Thyroid-stimulating hormone (TSH), (if required), fasting lipid profile (FLP) that will include Triglycerides (TG), Total cholesterol (TC), High-density lipoprotein-C (HDL-C), low-density lipoprotein-C (LDL-C), very low-density lipoprotein-C (VLDL-C). Standard laboratory techniques will be used to measure all the biochemical parameters, as mentioned below.

Treatment to patients during hospital stay like diuretics, ACE/ARB, beta-blockers, antiplatelet, statins, dopamine, dobutamine, nor-adrenaline, intubation will be noted. The outcome in the form of discharge, mortality and duration of hospital stay will be noted.

Follow up

Patients discharged from the hospital will be followed up telephonically or interviewed (medicine OPD) every two months for six months. The patient's history of mortality will be noted.

Plan of study

Patients having symptoms and signs of HF (according to Framingham heart failure criteria), which may be new onset or the result of decompensation of CHF (after undergoing inclusion & exclusion criteria) will be enrolled.

Patient will be subjected to undergo serum uric acid and electrocardiogram within 30 minutes of admission and 2D echo will be performed within 12 hours of admission.

Aetiology, risk factors, other lab parameters, and treatment received will be noted.

Outcome in form of in-hospital mortality, discharge and morbidity (length of hospital stay).

Follow up 2 monthly for six months after discharge to look for mortality (telephonically and/ or OPD).

Hazard ratio will be calculated to find out predictive value of serum uric acid in AHF.

Methods of anthropometric measurements

Blood pressure will be measured using a sphygmomanometer, an average of ≥2 readings obtained on ≥2 occasions in every participant in a sitting position will be used for interpretation. Weight (kg), height (m), and waist and hip circumference (cm) will be estimated using standardized devices and methods [13]. The person's bodyweight will be measured while standing still on the scale, feet apart, and weight uniformly distributed on both legs. Height will be measured with the subject standing with heels, buttocks, shoulders & head touching a vertical scale, and the head positioned in the Frankfurt plane in an upright position. The Quetelet formula will be used to compute BMI, which is weight in kg divided by height squared (m2) [kg/m2]. The circumference of the abdomen (waist) will be measured in a standing position of Study Participant (SP). The SP will be asked to hold up his/her clothes. A tape measure is aligned at the level of the belly button, to the maximum height of iliac crest and circle whole way around the body with the tape parallel to the floor and not compressing the skin. Waist measurements will be made at minimal respiration as the SP breathes out. According to the WHO STEPS procedure (WHO, 2008b) , the waist circumference is determined roughly in the middle between the inferior border of the last palpable rib and the tip of the iliac crest [14]. With the individuals standing straight, non-stretchable plastic tape will be used to measure neck circumference at the

halfway of the neck, between the mid-cervical spine and the mid anterior neck. It will be measured slightly below the prominence in men with laryngeal prominence. The patient will be asked to stare straight ahead while keeping their shoulders lowered but not dropped [15].

Statistical analysis

The Kolmogorov–Smirnov test will test all variables for normal distribution. Continuous variables have a normal distribution and are given as mean standard deviation (S.D.). Numbers (percentages) are used to express categorical variables. The Student's t-test and the evaluation of variation between independent groups will be used to make comparisons. The chi-square test will be conducted to analyze categorical data, and if necessary, Fischer's exact test will be used. There are two sides to each test. For the study of comparisons between UA rates and continuous variables, a single linear regression model will be used. To estimate their statistical importance, Kaplan–Meier cumulative survival curves will be created and Log values will be obtained.

The correlation between each baseline variable and mortality will be assessed using univariate Cox proportional risk analysis. To estimate the unusual predictive value of hyperuricemia, a stepwise multivariate Cox proportional analysis will be used. The multivariate model will contain fixed variables, which are known variables and predisposing factors, as well as variables with a p b 0.10 in the univariate analysis. At 95 percent confidence intervals, hazard ratios (HR) and their confidence intervals are indicated (95 percent CI). For statistical analysis, STATA data analysis and statistical software (STATA 14 programme) will be used.

DISCUSSION

Some of the earlier studies have summed that hyperuricemia (sUA >6.5 mg/dl) is related to an enhanced chance of HF, severe consequences in HF patients, as well as a nearly doubled mortality rate in HF patients. Nonetheless, hyperuricemia is linked to a forty three percent higher risk of the all mortality in patients with AHF [10].

The predictive significance of sUA may be influenced by the left ventricular ejection fraction (LVEF) of AHF. Concomitant hyperuricemia is directly connected to the associated outcome of mortality or readmission in patients with sustained LVEF [16]. While a low LVEF indicates a serious case of heart failure.

Renal function appears to be impaired in many heart failure patients, and it is also a most significant predictive indicator in HF patients. Raised uric acid levels in AHF may potentially be due to decreased renal clearance, ischemic renal dysfunction, and xanthine oxygenase upregulation [17]. Studies on different aspects of heart failure were reviewed [18-23]. The statistical model might have influenced the predictive importance of serum Uric Acid due to the absence of improvement in patients' medical history of gout, XOI or diuretic usage, increased urate production, and reduced renal function. In this study, we review the evidence relating sUA to HF prognosis.

CONCLUSION

Patients with AHF with a raised level of Serum Uric Acid considerably rise the jeopardy of dying from any reason. Ascertainment of SUA amount can enhance hazard substantiation of unfavourable consequences in patients with AHF. To determine whether xanthine oxidase inhibitors, uricosuric medicines, and uricase medications can improve the outcome of HF, large randomized controlled studies and clinical trials will be required in the future. Reducing uric acid is anticipated to be a new approach for the prevention and management of HF. As a result, the advantages of uric acid-lowering medication should be moreover reviewed within acute heart failure patients.

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